

# EXHIBIT D

**Rule 26 Report of Kimberly Kenton, MD, MS**  
**Board-certified, Female Pelvic Medicine & Reconstructive Surgery**

This is my report related to the safety and efficacy of Ethicon's TVT and TVT-O midurethral slings. My opinions relate to TVT™ and TVT-O™ being safe for its intended use in treating stress urinary incontinence and describing how the benefits of TVT™ and TVT-O™ significantly outweigh the risks associated with the procedure. All of my opinions are held to a reasonable degree of medical certainty, and I reserve the right to amend my report and opinions based on new information. I have reviewed the expert reports of plaintiffs' experts and have included my reliance materials as an attached exhibit.

**I. Background and Education:**

I am board-certified by the American Boards of Obstetrics & Gynecology and Urology in Female Pelvic Medicine & Reconstructive Surgery and by the American Board of Obstetrics & Gynecology in Obstetrics & Gynecology. My current position is Professor of Obstetrics/Gynecology and Urology, Division Chief of Female Pelvic Medicine & Reconstructive Surgery (FPMRS) at Northwestern University, Feinberg School of Medicine in Chicago, Illinois. I am an internationally recognized leader in Female Pelvic Medicine & Reconstructive Surgery/Urogynecology for my expertise in the clinical and surgical care of women with urinary incontinence and pelvic organ prolapse as well as high-quality surgical outcomes and comparative effectiveness research. I earned a Master of Science in Clinical Research Design and Statistical Analysis at the University of Michigan, Ann Arbor and served as the principal investigator on multiple NIH (National Institute of Health) grants studying urinary incontinence.

I was part of a multicenter group who designed, implemented and published the largest US comparative effectiveness trial comparing transobturator midurethral sling to the gold standard retropubic midurethral sling. This landmark study showed the efficacy and safety of both types of synthetic midurethral sling. Gynecare TVT™ was *intentionally* selected as the retropubic sling to be used in this study due to previously published large trials demonstrating efficacy and safety of the procedure and the mesh. I have over 170 peer-reviewed scientific research publications, many of which pertain to the etiology and treatment of urinary incontinence. Recently, the American College of Obstetricians & Gynecologists and the American Urogynecologic Society asked that I co-author a national Practice Bulletin summarizing current evidence for the evaluation and treatment of urinary incontinence in women. I also authored the bladder neck fascial sling section of UpToDate. UpToDate is the only clinical knowledge resource for physicians with research studies demonstrating improved outcomes. A subject matter expert and at least two different physician reviewers perform a comprehensive review of the literature and develop clear evidenced-based recommendations for treatment. Both documents support published randomized trial and meta-analysis data endorsing

midurethral sling as first line treatment for stress incontinence in women based on safety and efficacy.

## **II. Experience:**

My experience as a surgeon, educator, and researcher resulted in my leadership in our national certifying and credentialing organizations. The American Boards of Obstetrics & Gynecology and Urology selected me to serve on the joint Female Pelvic Medicine & Reconstructive Surgery Division charged with developing the exam to certify individual surgeons in FPMRS. I worked with a small group of six urogynecologists and urologists from across the US to write the exam used to credential sub-specialty surgeons performing surgery for urinary incontinence in women. Likewise, I was part of the team who worked with Accreditation Counsel of Graduate Medical Education (ACGME) to develop guidelines for fellowship training in FPMRS.

## **III. Board Certification:**

Board certification is a voluntary process and differs from medical licensure in that medical licensure sets minimum competency requirements to diagnose and treat patients; it is not specialty specific. Board certification demonstrates a physician's exceptional expertise in a particular specialty. In addition, the American Board of Medical Specialties [ABMS (parent board to ABOG and ABU)] requires that all certified physicians engage in on-going maintenance of certification to ensure they stay current of advances in the evaluation and treatment of patients by that specialty. Patients, physicians, health care providers, insurers and quality organizations look for these markers as the best measure of a physician's knowledge, experience, and skills to provide quality health care within a given specialty, recognizing the growing need for research and high-quality specialty care for women with urinary incontinence and pelvic floor disorders beyond that provided by urologists and gynecologists. The ABMS officially approved the specialty of **Female Pelvic Medicine and Reconstructive Surgery** in the spring of 2011. In so doing, ABMS acknowledged that care for women with complex pelvic floor disorders (such as urinary and fecal incontinence, and pelvic organ prolapse) requires subspecialty training and certification beyond the training acquired by a general obstetrician-gynecologist or a general urologist. In June of 2013, the American Board of Obstetrics and Gynecology and the American Board of Urology certified the first individual physicians. My CV is attached as Exhibit "A".

I am charging \$600 per hour for meetings and to review documents, \$700 per hour for deposition testimony, and \$4,000 per day for trial testimony. I have testified as an expert in the *Mullins v. Ethicon* case (Deposition testimony on February 18-19, 2016) within the past four years.

#### **IV. Professional Societies:**

I am also a member and have held leadership positions in all of our major professional organizations, including:

- American Urogynecologic Society where I served on, then chaired the Education Committee; the Board of Directors; Grant Review Committee; and Leadership Committee.
- Society of Gynecologic Surgeons where I served on the Research Committee; served then chaired the Education Committee; and the Executive Committee.
- American College of Obstetricians & Gynecologist where I served on the Practice Bulletins Committee for Gynecology and the Clinical Document Review Panel. Most recently, I chaired the committee responsible for the first Prolog in Female Pelvic Medicine & Reconstructive Surgery.
- Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction where I participated on a small work group who developed a urodynamics curriculum for urology residents.
- American Urologic Association.
- International Urogynecologic Society where I served on the Research & Development Committee.
- International Continence Society.

I devote my time and energy to these organizations as well as our certifying/credentialing boards (ABOG, ABU, and ACGME) because these organizations are *dedicated to improving health outcomes for women with urinary incontinence* and other pelvic floor disorders. Nearly all of the organizations dedicate significant resources to developing evidenced-based guidelines to help clinicians and patients chose the best health care treatments, which optimize outcomes and complications. In fact, most of the organizations (AUGS, SUFU, IUGA, and AUA) developed thoughtful, evidenced-based statements supporting the use of synthetic midurethral slings as a primary treatment for stress urinary incontinence in women. The mission of American Urogynecologic Society, the leader in FPMRS, is to “promote the highest quality patient care through excellence in education, research and advocacy.” The Society developed an evidenced based statement on role of midurethral slings and accompanying FAQs for providers and patients because of their commitment to *our patients*.

Learning how to perform surgery using the retropubic midurethral sling is listed as a learning objective in the AUA National Medical Student Curriculum dated August of 2012. Additionally, the AUGS Resident Learning Objectives suggest residents should “understand the differences between traditional and minimally invasive surgical approaches, e.g., open Burch versus laparoscopic Burch, and traditional pubovaginal

sling versus mid-urethral sling.” The resident should also be able to “discuss risks, benefits, and expected outcomes of nonsurgical and surgical management of SUI.” Moreover, the residents should “understand and perform a mid-urethral sling, using either retropubic or transobturator approach.” Residents are also expected to be familiar with synthetic foreign body materials, as they should “understand the vital characteristics of synthetic grafts, e.g., pore size, mono versus polyfilament, material types; understand the relative indications for, and complications associated with, each category of grafts; and understand the management of graft complications, both surgical and non-surgical.” The ACGME Competencies require fellows to demonstrate competence in performing surgery for urinary incontinence using synthetic slings. The ABOG and ABU Guide to Learning Female Pelvic Medicine and Reconstructive Surgery suggests that FPMRS fellows should be able to perform and describe the complications associated with synthetic retropubic slings and be able to manage complications associated with continence surgery, including: cystotomy, fistula, persistent or recurrent urinary incontinence symptoms, voiding dysfunction or retention, foreign body associated complications, and urinary tract infection. It is important to note that FPMRS fellows are also expected to cite published success and complication rates for each continence procedure, quality of studies, and level of evidence. Lastly, the IUGA Guidelines for training in FPMRS suggest that trainees should receive experience in the theory, practice, and performance of minimally invasive slings, mesh use in repairs, use of various graft materials, and sling procedures – retropubic, pubo-vaginal, mid-urethral and transobturator. As such, residents and fellows are expected to become familiar and keep current with the frequency and severity of complications associated with midurethral slings through their education, training, experience, and review of the medical literature.

I chose to use Ethicon TVT™, TVT™ Exact, and TVT-O™ for the primary surgical treatment of stress urinary incontinence in my patients who selected midurethral sling for over a decade because of the magnitude of the clinical data demonstrating their safety and efficacy. I have never received any financial support from Ethicon.

#### **V. Procedures Performed:**

I have regularly performed surgery to treat stress urinary incontinence since starting my ABOG/ABU accredited fellowship in 1999. First line surgical treatments of stress incontinence at that time were Burch colposuspension and bladder neck fascial sling. I performed countless numbers of both procedures, which involve an abdominal incision and are significantly more invasive than midurethral slings. From 2002-2004, I was part of a large federally supported comparative effectiveness trial comparing outcomes of Burch and bladder neck fascial slings, SISTEr (Stress Incontinence Surgical Treatment Efficacy Trial) directly comparing Burch and bladder neck fascial slings (Albo M. NEJM 2007). Unlike a case series evaluating autologous fascial slings, which is considered level 4 evidence, the SISTEr study provides level 1 evidence.

In 2000, the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) established the Urinary Incontinence Treatment Network (UITN), recognizing the need for well-designed outcomes studies for urinary incontinence treatment in women as previous studies had methodological flaws and/or limitations that precluded definitive conclusions about the relative efficacy or differences in complications between procedures. These limitations included variability in case definition, failure to account for known confounders, lack of standardization of technique, short duration of follow-up, poor generalizability, inadequate power to detect clinically important differences, lack of assessment of complications, and marked variability in outcome assessment (UITN. Urology 2005). Randomized controlled trials or comparative effectiveness trials are considered the best of all research designs because the act of randomizing patients to receive one intervention or the other ensures that, on average, all other factors are equal between the groups. Therefore, any significant differences in outcomes or complications between the groups can be attributed to the intervention or procedure and not to some other factor. Burch and bladder neck slings were selected for comparison by the UITN since they were considered the 'gold standard' procedures for treating stress incontinence in the US at that time; although expert opinion existed regarding the efficacy of the procedures, no prospective comparative data was available to support or refute "expert opinions". We now have 2-year and 5-year outcome and complication data directly comparing these two procedures (Albo M. NEJM 2007, Brubaker L. JAMA 2012).

I expanded my surgical counseling to include midurethral sling (Ethicon TVT™ in particular) in the mid-2000s based on evolving scientific data, in particular a 14-center randomized trial done in the UK comparing Ethicon TVT™ to Burch colposuspension (Ward KL. BMJ 2002, Ward KL. AJOG 2004, Ward KL. BJOG 2007). I later began offering TVT-O based on additional published data and participation in the development of a federally funded comparative effectiveness trial of transobturator and retropubic midurethral slings. Midurethral slings are less invasive, have fewer complications, (less prolonged voiding dysfunction, and result in quicker recovery times for patients. As part of a clinical research network supported by the National Institutes of Health, I helped design, implement and publish the largest US comparative effectiveness trial comparing Monarc and TVT-O transobturator midurethral sling to the gold standard TVT retropubic midurethral sling. This landmark study showed the efficacy and safety of both types of synthetic midurethral slings at 1, 2 and 5-years after surgery (Richter HE. NEJM 2010, Albo M. J Urol. 2012, Kenton K. J Urol 2015). Gynecare TVT™ was *intentionally* selected as the retropubic sling to be used in this study due to previously published large trials demonstrating efficacy and safety of the procedure and the mesh. At the start of the study period (similar to the UK study comparing TVT™ to Burch), only mechanically cut mesh was available, so these data reflect clinical outcomes of mechanically cut mesh. The 5 year TOMUS study is an accurate reflection of the long-term safety and efficacy of both TVT and TVT-O in my hands, which provides me with an extra level of confidence in claiming that my clinical experience in tracking success and complication rates are

comparable to the other level 1 scientific data evaluating both products, in part because I have contributed to the level 1 data.

I have performed over a 1,000 TVT™ (mechanically cut and laser cut) and TVT™ Exact (laser cut) procedures and currently offer retropubic midurethral slings as a first line procedure in women with stress urinary incontinence. I have also performed 250 TVT-O procedures. As a result, I have significant clinical experience with both mechanically and laser cut sling mesh. Similar to the large body of published clinical outcomes data – including over 100 RCTs, TVT long-term studies, TVT-O long-term studies, Cochrane Reviews, Registries, Meta-Analyses and Systematic Reviews – I have not found any clinically relevant differences in the design properties or outcomes suggesting clinically significant differences between mechanically cut and laser cut TVT or TVT-O. While theoretical and laboratory data may offer interesting hypotheses worthy of clinical studies, there are presently no substantial comparative clinical data in women with stress incontinence suggesting benefit of one over the other. Given the low rates of mesh exposures in well-designed published trials and long-term studies with follow-up ranging from 10-17 years using mechanically cut sling mesh, it is unlikely that comparative studies of mechanically and laser cut meshes will ever be feasible due to impractically large sample sizes that would be required to show a marginal difference, if any, between mechanically cut and laser cut TVT or TVT-O.

I continue to counsel each woman planning surgery for stress urinary incontinence about the full range of surgical alternatives, including Burch colposuspension, bladder neck fascial sling, and both retropubic and transobturator midurethral slings, but recommend Amid Type I polypropylene, macroporous synthetic midurethral slings, such as TVT and TVT-O, for the majority of my patients. Each procedure is associated with reasonable success rates, but differ with respect to complications and recovery time, and individual women should be allowed to select the risk profile that most suits her goals. Currently, the majority of my patients select the retropubic midurethral sling; however, some patients prefer a transobturator route. In particular, those with extensive prior retropubic surgery or in whom short-term urgency or voiding issues would be particularly bothersome.

Two recent systematic reviews (Ford AA. Cochrane Database Syst Rev. 2015, Tommaselli GA. Int. Urogynecol J. 2015) evaluating the safety of retropubic and transobuturator midurethral slings concluded that ‘midurethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term and accruing evidence demonstrates their effectiveness in the long term.’ When comparing transobutator and retropubic approaches, the authors of the Cochrane Review found that there were no statistically significant differences in rates of overall perioperative complications between the procedures. Overall, vaginal mesh exposures were not different for retropubic or transobturator midurethral slings (approximately 2%). Similarly, no differences in

vaginal erosions were observed between TVT-O (medial to lateral) and lateral to medial transobturator approaches. Rates of postoperative pain were low with both transobturator and retropubic midurethral slings (4.5%), and when pain was reported the 'occurrences were short lasting, with most resolving in the first 6-months'. Tommaselli found no differences in postoperative pain (OR 0.78) nor persistent voiding dysfunction (OR 1.23) between retropubic midurethral slings or transobturator midurethral slings. Similarly, no differences in these complications were observed between TOT and TVT-O. The authors concluded that the similar efficacy of retropubic and transobturator midurethral slings is "backed by a high safety profile, and by a limited number of complications which were seldom severe." Although mesh exposure/erosion is commonly viewed as the only unique complication associated with TVT and TVT-O compared to other surgical treatments for SUI, Burch and Autologous fascial sling studies have reported erosions.

However, in select women who decline or are not candidates for synthetic mesh slings, bladder neck fascial slings remain an important, effective treatment option. Several conditions in which autologous fascia sling should be considered include:

- Women with severe stress incontinence and a non-mobile, fixed urethra, bladder neck sling may be preferable due to its slightly more obstructive nature. Some surgeons will place a bladder neck fascial sling under more tension (more obstructive) than a synthetic sling secondary to risks of urethral erosion.
- Women undergoing urethral reconstruction (eg: diverticulectomy or fistula repair) should be considered for concomitant bladder neck slings. Several investigators reported good incontinence outcomes and low complication rates after urethral diverticulectomy and autologous fascial sling.
- Women who had complications from prior mesh placed in the anterior vagina (for incontinence or prolapse) may be candidates for autologous fascia sling. Several case series report good outcomes with removal of prior mesh and/or placement of autologous fascia sling (Milose JC. J Urol. 2015); however, multiple studies also report good outcomes when a second synthetic midurethral sling is placed (Pardon AM. Obstet Gynecol. 2013).

Although the aforementioned patients may benefit from a bladder neck fascial sling, the majority of patients seeking surgical treatment for uncomplicated stress incontinence are best suited for a synthetic midurethral sling. The bladder neck fascial sling has its place in a surgeon's armamentarium, but should not be considered the gold standard procedure secondary to increased complications and recovery. Historically, bladder neck fascial slings were reserved for women with 'intrinsic sphincter deficiency' or severe stress incontinence, while Burch was the first line treatment. The limitation of this treatment strategy was related to diagnosis of intrinsic sphincter deficiency. Numerous clinical investigators tried over the years to determine which patients should get bladder neck slings and which Burch colposuspension using various measure of urethral function (Valsalva Leak Point Pressures, Maximum Urethral Closure Pressures,

Electromyography) to diagnose intrinsic sphincter deficiency. Unfortunately, NONE of the measures discriminated surgical success/failures, thus limiting their clinical utility. To date the BEST comparative data available is the UITN's SISTER study, published in the New England Journal of Medicine. Within the last 10 years, the synthetic midurethral sling has replaced traditional, more invasive abdominal procedures as the gold standard for the primary surgical treatment of stress incontinence. In the 2 year SISTER data, there were 20 patients out of 326 (6.1%) who had voiding dysfunction that lead to surgical revision; in contrast in TOMUS (comparing retropubic and transobturator slings), which was designed and implemented by the same clinical sites and surgeons as SISTER experienced rates of voiding dysfunction leading to surgical revision that were < 2.7%. TOMUS data are similar to recent well designed meta-analyses that report retention lasting longer than 6 weeks after surgery is approximately 2.5% after midurethral slings (obturator and retropubic) and 7.5% after bladder neck slings. Additionally, erosion and sling exposures are reported after rectus fascial bladder neck slings. Authors of a three year follow-up study reported outcomes of a series of women who underwent rectus fascial sling in which 2 patients (0.8%) had a vaginal sling erosion requiring surgical intervention and 5 (1.9%) had a wound infection (Athanasopoulos A. Urology 2011).

#### **VI. Overview of Stress Urinary Incontinence:**

Urinary incontinence affects 10–70% of women living in a community setting and up to 50% of nursing home residents and is often the main reason for nursing home admission. Prevalence of incontinence increases gradually during reproductive years peaking around middle age, and then steadily increasing with aging (DuMoulin MF. Scandinavian J Caring Sci. 2009, Offermans MP. Neurourol Urodynam. 2009). Despite the prevalence of urinary incontinence, many women are hesitant to seek care or discuss their symptoms with a health care provider. In a survey of women in the United States, only 45 percent of women who reported at least weekly urine leakage sought care for their incontinence symptoms (Hannestad YS. J Clinical Epi 2000). As a result, many incontinent women live with physical, functional, and psychological limitations and diminished quality of life at home and at work.

In 1995, the estimated annual direct cost of urinary incontinence in the United States was \$12.43 billion (Wilson L. Obstet Gynecol. 2001), which was greater than the annual direct costs for breast, ovarian, cervical, and uterine cancers combined (Varmus H. Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support. Bethesda (MD): Department of Health and Human Services, National Institutes). In 2001, the demand for treatment for pelvic floor disorders was estimated to increase by 45% over the next 30-years with a commensurate rise in health care costs (Luber KM. AJOG. 2001). In the United States in 2010, approximately 260,000 women underwent surgical treatment of stress urinary incontinence (Urogyn surgical mesh update, FDA July 2011). Stress urinary incontinence affects 16% of adult women with 78% reporting their symptoms to be bothersome and with nearly 30% reporting their symptoms to be

moderately to extremely bothersome. In 2010, approximately 260,000 women in the United States underwent surgical treatment of SUI (ACOG/AUGS Committee Opinion No. 603, 2014).

Since their introduction in the 1990s, midurethral slings have become the primary surgical treatment for stress urinary incontinence in women with a 27% increase in the rate of surgical management of stress urinary incontinence from 2000 to 2009, the majority of which was secondary to increase in number of sling procedures (Anger JT Urol 2009, Jonsson Funk M Obstet Gynecol 2012). Additionally, published surveys and literature have shown a significant increase in synthetic midurethral slings, which corresponds with a sharp decline in the usage of autologous fascial sling and Burch procedures over the past ten years. A 2015 Cochrane Review of the peer-reviewed literature concluded that “midurethral sling operations are the most extensively researched surgical treatment for stress incontinence in women, have a good safety profile.... and are highly effective in the short and medium term... accruing evidence demonstrates their effectiveness in the long term.” (Ford AA. Cochrane Database Syst Rev. 2015). The authors also conclude that midurethral slings have a “positive impact on improving quality of life of women with stress incontinence.” Ford reported the following complication rates from registries for the retropubic midurethral sling: bladder perforation 2.7 – 3.9%, reoperation rates relating to tape insertion or postoperative voiding dysfunction 1.6% - 2.4%, urinary retention rate was 1.6%, pelvic hematoma 0.7% - 1.9%, infection rate was 0.7%, vaginal tape erosion/extrusion rate was 1.5%, groin pain occurred in 0.4% of women. Similar rates were reported for transobturator slings: bladder perforation 0.4%, reoperation rates relating to tape insertion 0.8% - 2.2%, urinary retention 0.5%, pelvic hematoma 0.5%, infection rate 0.6%, vaginal tape erosion/extrusion rate was 0.4%, and groin pain occurred in 1.6% of women. These rates are consistent with the FDA’s analysis of complication rates from the MAUDE database showing around 2% mesh exposure, and the Medicines and Healthcare Products and Regulatory Agency (MHRA) in Europe publishing a low vaginal tape erosion rate between 1.1% to 2.5%. In their 2014 report, the MHRA concluded that there appeared to be no evidence that vaginal mesh implants for SUI are unsafe.

Another meta-analysis of 62 randomized trials concluded that midurethral slings are as effective as Burch colposuspension and bladder neck fascial slings, but are associated with shorter operative times, quicker recovery, and fewer postoperative complications (Ogah J. Cochrane Database Syst Rev. 2009 and 2011). Short-term cure rates of midurethral slings were comparable to bladder neck sling (73% vs 71%, RR 1.0 95% Ci 0.9-1.1), open Burch colposuspension (79% vs 82%, RR 1.0, 95% CI 0.9-1.0), and laparoscopic colposuspension (82% vs 74%, RR 1.1, 95% CI 1.0-1.2). Rates of new onset urgency and urgency incontinence are **lower** after midurethral sling compared to bladder neck slings.

Several large multicenter trials compared retropubic and transobturator midurethral slings (Richter HE. NEJM. 2012). The Trial of Midurethral Slings (TOMUS) randomized women with stress predominant urinary incontinence to TVT™ (mechanically cut mesh) or transobturator midurethral slings. Using a composite primary outcome (negative cough stress test, negative pad test, no retreatment, no self-reported symptoms, and no leakage episodes on voiding diary) the procedures were equivalent (81% for TVT™ and 78% for transobturator) at one-year. However, at 24 months, neither objective nor subjective success rates met the predefined criteria for equivalence. Voiding dysfunction was more common with retropubic slings (2.7% vs 0%), but neurologic symptoms were more common with transobturator slings (9.4% vs 4.0%). The most common adverse effect was UTI (26%). ***Mesh complications (3.4%) were uncommon (16 exposures and 2 erosions) in the first 2-years.*** There were only 7 new mesh erosions (3 TVT™, and 4 transobturator slings) between year 2 and 5.

The Ogah Cochrane Review evaluated 7,101 women across 62 trials. This level 1 meta-analysis found that minimally invasive midurethral synthetic slings, such as TVT and TVT-O, were as effective as traditional suburethral slings, but had the benefit of having shorter operating time, less post-operative voiding dysfunction, and less de novo urgency symptoms (Ogah J. Cochrane Database Syst Rev. 2009 and 2011). Similarly, synthetic midurethral slings were as effective as open Burch procedures, but with fewer perioperative complications, less post-operative voiding dysfunction, and shorter operative time and hospital stay; however, the TVT had more bladder perforations. The Ogah Cochrane Review also found that TVT was more effective than top-to-bottom (Sparc) route and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. There was no statistically significant difference between retropubic and transobturator slings.

While urethral bulking agents are rarely used as a primary treatment for stress urinary incontinence, they remain an option for women with persistent stress urinary incontinence or women with commodities who cannot tolerate anesthesia or surgery. A recent Cochrane Review found that urethral bulking agents are less effective than sling surgery with 1.7- to 4.7-fold increased likelihood of cure with surgical treatment.

## **VII. Alternative Treatments for Stress Incontinence:**

### ***A. Pelvic Floor Muscle Exercises***

Pelvic floor muscle exercises are effective treatment for stress incontinence. Approximately half of women with stress predominant urinary incontinence are satisfied one year after starting pelvic floor muscle training. A recent trial compared pelvic floor muscle training to midurethral sling for treatment of stress urinary incontinence. Forty-nine percent of women in the pelvic floor muscle-training group crossed over to surgery and 11% of women in the surgery group crossed over to physical therapy. In intent to treat analysis, subjective cure rates were 85% in the surgery group

and 53% in the physical therapy group suggesting initial midurethral sling surgery results in higher cure rates than physical therapy at one-year.

#### ***B. Incontinence Pessaries***

Incontinence pessaries can improve stress urinary incontinence symptoms in some women by increasing urethral resistance. One randomized trial demonstrated similar satisfaction with stress incontinence symptoms one-year after pessary and behavioral-physical therapy (Richter HE. Obstet Gynecol 2010). There was no benefit to combined therapy with pessary and behavioral-physical therapy. Health care providers should discuss both pessary and behavioral-physical therapy as effective conservative therapies for stress urinary incontinence. Patients will likely select based on personal factors; pessary offers more immediate symptom control, while physical therapy may offer long-term neuromuscular changes.

#### ***C. Behavioral Modification***

Level I evidence exists supporting role of some behavioral modifications in the treatment of urinary incontinence. In one study, behavioral therapy including group and individual instruction, scheduled voiding, diary keeping, and pelvic floor muscle exercises resulted in a 50% reduction in mean incontinence episodes compared with a 15% reduction in controls. Behavioral training with biofeedback did not reduce incontinence episodes more than providing verbal feedback or receiving a self-help booklet. Therefore, behavioral therapy improves symptoms of urinary incontinence and can be recommended as a noninvasive treatment in many women.

Obesity is an independent risk factor for the development of incontinence, with obese women having a 4.2-fold greater risk of stress urinary incontinence than those with a normal body mass index. Several trials demonstrate that moderate weight loss can improve stress urinary incontinence symptoms in overweight and obese women suggesting that even moderate weight loss can improve stress urinary incontinence symptoms.

#### ***D. Urethral Bulking Agents***

While urethral bulking agents are rarely used as a primary treatment for stress urinary incontinence, they remain an option for women with persistent stress urinary incontinence or women with comorbidities who cannot tolerate anesthesia or surgery. A recent Cochrane Review found that urethral bulking agents are less effective than sling surgery with 1.7- to 4.7-fold increased likelihood of cure with surgical treatment.

#### ***E. When to Recommend Surgical Treatment***

Surgery is indicated for appropriately counseled women with stress urinary incontinence who decline or have insufficient symptom control after conservative treatment. While surgical treatments are associated with higher success rates than conservative therapy, surgery is also associated with increased morbidity, postoperative voiding difficulty and development urgency incontinence. Recent randomized trial data

demonstrate a higher subjective improvement (91% vs 64%) and objective cure rates (77% vs 59%) one-year after midurethral sling compared to physical therapy, suggesting midurethral sling is an appropriate first-line treatment in appropriately counseled women. Each woman must balance her symptom bother, quality of life impact, and goals for treatment when deciding upon surgical management of her stress urinary incontinence. The projected total number of women who will undergo SUI surgery will increase 47.2% from 210,700 in 2010 to 310,050 in 2050. (Wu J. AJOG 2011).

***F. Laser cut vs. mechanically cut mesh***

I regularly review the medical literature related to surgical procedures and devices used to treat stress urinary incontinence, and I have never seen any clinical outcome literature that would suggest mechanically cut mesh is inferior or causes complications; nor have I seen any literature suggesting that laser cut is superior and causes fewer complications.

The edges of mechanically cut TVT™ mesh are not sharp and do not cut into tissue and cause complications. The unsealed edges provide for greater tissue integration through the ‘Velcro effect’. I have read literature in which the authors speculated and theorized about differences in the cut of the sling being a contributing factor to complication rates, but this is nothing more than conjecture. An example of such is from a 2011 comparative study evaluating TVT™-O (mechanically cut) and TVT™-Secur (laser cut), the authors hypothesized that higher rates of dyspareunia in the TVT™-Secur group may be explained “in part by the rigidity and reduced flexibility of the synthetic polypropylene implant because it is laser cut, which tends to result in a stiff tape edge. As a result, the overlying vaginal mucosa is constantly traumatized, much more than it would be with use of mechanically cut tape.” (Neuman M. J Minimally Invasive Gynec. 2011).

Another example of such conjecture by authors is a study comparing Advantage, which has a laser cut section, to mechanically cut TVT, in which the authors suggested that the heat-treated section of the Advantage sling made the tape stiffer and less elastic in animal and in vitro studies (Lim YN. Int. Urogyn. J 2010). They theorized that the increase in overactive bladder and voiding difficulty issues with the Advantage “could be related to the slightly stiffer nature of the Advantage sling.” Moreover, the authors noted that TVT “is commonly acknowledged as the gold standard of MUS by virtue of its extensive safety and efficacy data in the literature.” Regardless, 93.2% of TVT patients and 92.6% of Advantage patients would recommend the procedure to a friend. In yet another example, in a different study comparing Lynx to TVT, the authors found an increased rate of vaginal mesh exposures with Lynx (4% with Lynx vs. 0% with TVT) and **wondered** if “the heat sealed edges in the Lynx system increased its resistance to deformation, thus increasing the risk of erosion.” (Agarwala. UroToday Int. J. 2008). They suggested that “the open weave Prolene [TVT] mesh also has unique biomechanical properties with low stiffness and low resistance to deformation, which

may be the reason for its low risk of erosion.” Again, patient satisfaction rates were similar at 92% for both products.

Furthermore, I am also aware of an internal email from an engineer at Ethicon who suggested that laser cut mesh would cause mesh to lay flat and reduce roping and curling, which would then reduce retention rates. Unfortunately, this theory is not substantiated in the peer-reviewed literature, nor have I noticed a difference in retention rates in my patient after placement of mechanically cut or laser cut TVT™ mesh. Likewise, I have also seen a company document suggesting that laser cut TVT™ mesh is 3 times stiffer than mechanically cut mesh when it was subjected to benchtop testing under strain, and the suggestion that stiffer mesh causes an increase in complications, such as pain and mesh exposure. Again, this is an unsubstantiated theory that would suggest a design change is warranted based on clinical data, or that laser cut results in statistically significant lower adverse events. I have not seen a difference in complication rates in the literature or my patients. I do not rely on internal company emails to guide my evidence-based clinical decisions. Plaintiffs’ experts’ opinions about a possible causal link between mechanically cut or laser cut causing complications are contradictory, misleading, and scientifically unreliable.

**VIII. TVT is Reasonably Safe for its Intended Use in Treating SUI: Supported by Cochrane Reviews, Meta-Analyses, Systematic Reviews, RCTs, Prospective and Retrospective Clinical Cohort Studies, Practice Patterns and Surveys, Society Position Statements and Guidelines, Review Articles, Medical Textbooks, My Clinical Experience, Education, My Review of the Medical Literature, and My Discussions with Thought Leaders:**

1. Midurethral slings are the most extensively researched surgical treatment for stress incontinence in women. They have a good safety profile and are highly effective in the short and medium term with accruing evidence demonstrating their effectiveness in the long term.
2. The midurethral sling has replaced alternative procedures (Burch colposuspension and bladder neck fascial sling) as the gold standard, first-line, surgical option for treating stress urinary incontinence. The peer reviewed medical literature and major medical professional societies support the position that polypropylene midurethral slings are the preferred surgical treatment option for stress urinary incontinence over Burch colposuspension and bladder neck fascial slings in most women based on efficacy and safety data.
3. Although controversy exists over the role of synthetic mesh using in vaginal repair of prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral sling as a primary treatment option for stress incontinence in women. For this reason, and to clarify the uncertainty for

patients and health care providers, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a position statement recognizing polypropylene mesh slings as the 'standard of care' in the surgical treatment of stress incontinence.

4. Midurethral sling surgery results in higher subjective and objective cure rates than pelvic floor physical therapy and pessary use in women with stress urinary incontinence.
5. Ethicon's TVT™ and TVT-O™ have a good safety and efficacy profile for treatment of stress incontinence in women, as evidenced in multiple randomized comparative effectiveness trials.
6. The benefits and utility of midurethral sling, including TVT™ and TVT-O™ significantly outweigh the potential risk of harms in most women who desire surgical treatment of stress incontinence.
7. TVT™ has been safely for over 17 years. TVT™ and TVT-O™ are safe and effective in a variety of patients with similar results from a wide range of surgeons and patients. A significant number of RCTs, long-term studies, and Cochrane Reviews have shown that retropubic midurethral sling is reasonably safe for its intended use. Since its introduction as a minimally invasive procedure, the TVT and TVT-O have grown rapidly in popularity as a first line treatment of stress urinary incontinence. The TVT and TVT-O have also shown excellent results in patients with previous failed incontinence surgery, intrinsic sphincter deficiency, and mixed incontinence. The reasons behind this success story include the relative ease of performing under local or regional anesthesia, outpatient procedure, good success and satisfaction rates, low complication rates, decreased postoperative pain, and fast recovery.
8. The medical literature does not support the theory that a change in the design of TVT™ or TVT-O™ would reduce or eliminate the already low mesh complications (2-3%) associated with TVT™ mesh, while also maintaining high cure rates.
9. The properties and characteristics of the TVT™ and TVT-O™ mesh are appropriate and desired for the intended use of treating stress urinary incontinence. The TVT™ mesh is classified as an Amid Type I, macroporous, polypropylene, monofilament mesh, and its safety profile is supported by numerous medium to long-term clinical studies. The vast body of clinical literature evaluating TVT™ and TVT-O™ has demonstrated that the design of TVT™ is appropriate and desired as a result of the excellent outcomes regarding safety, patient satisfaction, and efficacy. Studies have shown that the Prolene mesh used in the TVT mesh has lower complications than the Amid Type III meshes that were previously used, such as Gore-Tex, Mersilene, and Teflon. The

Ford 2015 Cochrane Review confirmed that “Type 1 mesh [like TVT and TVT-O] has the highest biocompatibility with the least propensity for infection.” They explain that “macroporous meshes (pore size in excess of 75 microns) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection.”

10. Current clinical outcome data in women with stress incontinence suggest that mechanically cut mesh is safe and effective as the majority of randomized trial data and long-term studies include mechanically cut TVT™ and TVT-O™ mesh. The way the mesh is cut does not seem to have a clinically significant impact on the mesh in actual women having surgery for stress incontinence. The TVT™ mesh is such that the 1.1cm width of tape allows for sufficient construction of pores that are able to provide the necessary tissue integration and support under the midurethra. The TVT™ mesh is appropriate for handling and lays flat under the midurethra. The theory that a 1.1cm strip of a lighter weight, larger pore mesh would provide the same lasting support without roping or curling is not supported in the clinical literature. The TVT mesh pore size allows for the intended tissue ingrowth which prevents pore collapse and does not foster shrinkage or contraction (Nilsson CN. *Int Urogyn J* 2013; Lo T. *Adult Urology* 2004; Lukacz, Lubner, Nager. *Int Urogyn J* 2003; Rinne K. *AOGS* 2011).
11. Based on outcome literature, the pore size and weight of TVT mesh is appropriate and acceptable for balancing success rates and complications for treating stress incontinence. TVT is classified as an Amid Type I macroporous mesh, which is the generally accepted classification for biomaterials. The effective porosity theory adopted by plaintiffs’ experts is not generally accepted in the SUI literature or by experts in the field of gynecology, urogynecology, or urology. TVT™ and TVT-O™ are often referred to as a large pore, lightweight mesh in the medical literature pertaining to SUI. Given the small 1.1 cm width of the TVT mesh, the mesh construction, pores, and weight are ideal for supporting the midurethra and allowing for tissue ingrowth. Any suggestion that changes would improve patient outcomes and reduce complications, while maintaining or improving clinical efficacy are unfounded and not supported by RCTs or clinical literature. Complications do not occur at an increased frequency because of the pore size or weight of TVT™.
12. All surgical procedures are associated with risks and complications. The complications associated with TVT and TVT-O are acceptably low and consistent across the vast body of level 1 medical literature. Just because a patient experiences a complication does not mean that TVT™ is defective. No device or surgical procedure is perfect, but the mesh used in TVT™ is the best studied surgical procedure for treatment of stress urinary incontinence. Complications

can occur due to surgical technique and various patient factors, which can also influence wound healing complications, such as mesh exposure.

13. All surgeries have risks and surgeons must help individual patients weigh her risk profile. Mesh exposures are complications unique to synthetic midurethral slings compared to native tissue repairs and occur in approximately 2-3% of women in the first 2-years after surgery; however, most mesh complications are easy to manage and many exposures are asymptomatic requiring no intervention. Voiding dysfunction, persistent retention, and urinary tract infections are complications that are more common after bladder neck fascial slings.
14. Native tissue repairs with permanent or absorbable sutures can also result in suture exposures and erosions, which could require a re-operation or simple office excision of the exposed or eroded suture.
15. Lighter weight, larger pore meshes have not been shown to be safer or more effective than TVT™ or TVT-O™ in comparative clinical studies or RCTs.
16. Post-operative chronic pain and dyspareunia are rare complications associated with both the retropubic and transobturator midurethral sling (Schimpf M. SGS 2014). In a randomized trial of 565 women undergoing TVT™ or transobturator sling, only 2% of those undergoing TVT™ reported any pain beyond 6-weeks after surgery. Pelvic pain and dyspareunia are common conditions among the general population, even for women who haven't undergone pelvic surgery, and have also been reported in the medical literature for traditional procedures. (Mathias S. ACOG 1996; Jamieson DJ. ACOG 1996; Francis W. J Obst and Gynec of the British Commonwealth 1961; Glatt AE. ACOG 1990; Laumann EO. JAMA 1999; Ozel B. Int Urogyn J 2005; Barber MD. ACOG 2002). TVT has been shown to improve sexual function. (Jha S. Int. Urogyn J 2009; Jha S. J. Sex Med 2011).
17. The complications, as well as the frequency and severity of those complications associated with TVT and TVT-O are known and acceptable to pelvic floor surgeons performing surgeries to treat stress urinary incontinence. The SGS Systematic Review shows TVT and TVT-O with lower rates of pelvic pain and dyspareunia compared to Burch and the Autologous Fascial Sling (Schimpf M. SGS 2014).
18. TVT™ fraying is not a defect. The frayed edges may help with tissue integration and there are no clinical implications associated with mesh fraying. There are no studies that have shown an increase in adverse events due to fraying of mechanically cut mesh. The laser cut TVT-Exact also has the potential to fray. I have not seen in my clinical practice or in the literature, any clinically significant

difference in complications or success rates between mechanically cut and laser cut mesh.

19. Several long-term studies on TVT™ and TVT-O™ would have been mechanically cut TVT, and they all have shown that TVT™ remains safe and effective for over 10 years. These results are consistent with Nilsson's 17-year results.
20. There is no objective clinical evidence that particle loss occurs in vivo. I have not seen particle loss in my practice in the more than 1,000 synthetic midurethral slings, I have placed, nor have I seen any medical literature showing a clinically or statistically significant increase in complications due to hypothetical particle loss.
21. TVT™ and TVT-O™ do not undergo clinically significant degradation in vivo. There is no peer-reviewed clinical literature, including randomized controlled trials, that supports the theory that TVT degrades, loses particles, ropes, frays or curls in women over time, or that there are clinically significant risks of degradation. I am not aware of any peer-reviewed published literature that shows any risks or complications associated with theoretical degradation nor am I aware of any professional organizations or content experts who have expressed a concern with degradation associated with TVT or TVT-O. The clinical studies (such as Clave's study) plaintiffs' experts rely on to suggest in vivo degradation occurs with TVT are flawed and do not confirm in vivo degradation, nor do they show an increase in clinically significant complications caused by degradation, or how much degradation is required to cause harm.
22. Burch colposuspension and bladder neck fascial sling remain appropriate surgical options in carefully select women, such as those with occult stress incontinence; those undergoing concomitant urethrovaginal fistula or diverticulum; those with prior mesh complications and/or failed midurethral sling; or those who do not want mesh. The current literature supports repeat midurethral sling after a failed midurethral sling.
23. I have performed a search of the literature and have not found any clinical studies or level 1 evidence that attributes any clinically significant risks associated with mechanically cut mesh fraying, roping, curling, particle loss, or degradation; or with laser cut being stiffer and causing more erosions and exposures.
24. The biomechanical properties and foreign body reaction of Prolene have been well-studied for almost 50 years as a suture and a mesh. Polypropylene is an appropriate material for use in clean contaminated surgeries.

25. Inflammation is not a complication. Inflammation is a necessary mechanism of tissue healing. Clinical studies have shown ideal tissue reaction with TVT (Falconer C. Int Urogyn J 2001).
26. The FDA performed a literature review of midurethral slings and found that full-length slings, such as TVT and TVT-O, were safe and effective.
27. The effect of attorney advertisements has caused significant confusion among patients. Numerous patients enjoying the benefits of continence with NO adverse complications after midurethral sling seek medical consultation secondary to concerns over 'recalled mesh' after being approached by lawyers or seeing advertisements (Perkins CE. Curr Bladder Dysf Rep 2015). AUGS members have expressed their concern for their patients who are being contacted (usually by phone) by individuals unknown to them asking them personal questions about their gynecology surgery (Nager C. AUGS Blog 2014). AUGS received 202 responses with 92% indicating that their patients had been contacted by an external source encouraging them to participate in a medical device lawsuit. The majority were contacted by phone after their surgery (96%). The caller knew the patient's name and procedure-specific information. The 2015 AUA Monograph found that, "[m]edia attention and publicly advertised personal injury lawyers' ad campaigns have led to confusion, fear, and negative perception regarding the use of synthetic material for treatment of SUI. The medical community generally has not shared the negative perception of synthetic mid urethral slings." The Monograph went on to note that:
- One of every three women will experience Stress Urinary Incontinence (SUI) at some point during their lives. Too many of them "live with" the condition, too embarrassed to seek help or thinking that it is a "normal" part of aging and having children.
  - SUI can interfere with quality of life. It may affect day-to-day decisions about social activities.
  - The Burch Colposuspension is a more invasive surgical procedure that has become less popular with the advent of the less invasive sling procedures.
  - Slings are the most commonly used surgery for SUI. Today, synthetic polypropylene mesh slings are the most common operation performed for SUI worldwide. One advantage of synthetic slings is a faster recovery time for patients.
  - There is support for the use of synthetic materials to treat SUI with minimal morbidity compared to alternative surgeries. There are

advantages regarding surgical recovery, need for hospitalization, and reduced problems with urination. However, there are certain mesh-specific complications that can occur but in most patients the risks are considered acceptably low. These mesh-specific complications include prolonged pain (1%), vaginal exposure of the mesh (1-2%) and erosion into the urinary tract (urethra or bladder) (< 0.01%).

28. No clinical evidence exists supporting the idea that the Prolene mesh used in TVT™ and TVT-O™ is cytotoxic and causes cell death in vivo, or is associated with malignancy that causes an increase in complications or a decrease in efficacy. There are no reported cases of TVT being causally linked to any cases of cancer (Moalli P., Nager C. Int Urogyn J 2014; King A, Goldman H. Curr Urol Rep 2014; Linder BJ. Int Urogyn J 2016; AUGS/SUFU FAQs for Providers 2014).
29. Retropubic midurethral slings have equivalent, if not superior, long-term success rates compared to Burch colposuspension and autologous fascial sling.
30. I have explanted various meshes as well as TVT™ and TVT-O, and I have not seen any migrating particles or TVT mesh that was degraded based on an observation with the naked eye. If any surface cracking or alleged degradation is going to be observed, it would be misleading to suggest that one could see signs of degradation that require SEM imaging or analytical tests to visualize or confirm.
31. In my experience with implanting and explanting TVT and TVT-O, I have not seen loose particles, fraying, or degraded mesh. I have used both mechanically cut and laser cut TVT and TVT-O, and I have not noticed a difference with the properties of the mesh or complications. I have seen company documents that refer to laser cut meshes as being stiffer which could cause more complications, but that is not what I have seen in my clinical practice or the medical literature. I have also seen internal documents that suggest mechanically cut mesh frays, ropes, curls, and causes particle loss, but I have not seen that in my clinical practice or in the clinical literature. Nor have I seen an increase in complications in my patients or in the clinical literature due to TVT being mechanically cut as opposed to laser cut. Further, I have also seen internal documents that suggest laser cut meshes could the mesh to lay flat and reduce retention, but I have not seen an increase in retention or meshes that aren't laid flat under the midurethra with mechanically cut TVT. Both mechanically cut and laser cut TVT meshes have the potential to fray if they are misused or stretched beyond clinically relevant forces under extreme testing; however, they function the same when used as intended in clinical use for treatment of SUI.
32. High volume surgeons have reduced complications, and implanting surgeons are more often than not informed if their patient has a complication through or referral or by re-operating on the patient (Welk B. JAMA 2015). In the recent

Welk study, out of 59,887 women who underwent mesh based procedure for SUI, only 2.2% were treated for complications and the 10 year cumulative incidence rate was 3.29%. Welk and colleagues found that “[t]he cumulative incidence of mesh removal or revision increased from 1.2% after 1 year of follow-up to 2.5% after 10 years of follow-up. The risk of surgical revision or removal of incontinence mesh is relatively rare, but does increase with time to 2.5% after 10 years of follow-up. Patients of high volume surgeons are significantly less likely to experience complications, and women who have undergone multiple sling placements are at much higher risk of experiencing these complications.” Other studies report a sling revision rate of 2.7%, with a median time of revision from the index surgery to the revision surgery of 7.8 months and 3.7% cumulative risk over 9 years (Unger CA. *Int Urogyn J* 2015; Jonsson-Funk M. *Obstet and Gynecol* 2013). A Kaiser Permanente analysis from Nguyen and colleagues found that mesh-related reoperations after sling procedures were performed for voiding dysfunction or urinary retention (49 of 3,747 [1.3%]), vaginal mesh erosion (30 of 3,747 [0.8%]), and urethral erosion (3 of 3,747 [0.08%]) (Nguyen JN. *ACOG* 2012). According to Nguyen, excision due to pain occurred in 0.04% [1 of 2,339] of retropubic midurethral slings and 0 of 794 in the transobturator group. Similarly, the sling complication was treated by the same implanting surgeon in 62.1% of the cases. The Schimpf SGS systematic review reported low complication rates with TVT and TVT-O based on a systematic review performed by the SGS. Case reports and case series, such as the Abbott 2014 case series is unreliable, biased, and should not be relied upon to extrapolate complications to an entire population given the small patient population, bias, and low level 4 case series evidence. Further, level 4 case series and case reports do not represent appropriate evidence based medicine for making clinical decisions.

33. Groin or leg pain with TVT-O is usually transient and typically resolves in the post-operative period. The literature has shown that while TVT-O has a higher rate of groin pain than TVT in the immediate post-operative period, the groin pain rarely persists in the long-term. At 7.5 year follow-up, Athanasiou (*Int Urogyn J* 2014) found that no patients reported persistent groin pain at the long-term follow-up. Similarly, Serati (*European Urology* 2013) and colleagues found that 9.9% of patients complained of groin pain 24 hours after the TVT-O procedure, while 3.1% complained of groin pain at six month follow-up, 1% at one year follow-up, and at 5 years, no cases of groin pain remained.

**IX. TVT and Synthetic Midurethral Slings Have Replaced Traditional Procedures as the Gold Standard Surgical Treatment for Stress Urinary Incontinence:**

Even as early as 2002, an IUGA survey showed that the procedure of choice for stress incontinence was TVT (48.8%), followed by Burch colposuspension (44%), and suburethral or autologous fascial slings used 3.8% as a primary procedure (Davila GW. Int Urogyn J 2002).

In a 2005 publication analyzing practice patterns of AUGS members, the authors described a study which reported a prevalence of sexual dysfunction in 48% of patients presenting to a urogynecology clinic (Pauls RN. Int Urogyn J 2005). Pelvic surgery may also increase this risk. Although most reports suggest improvement of sexual function following hysterectomy, there are some patients who may report negative changes postoperatively. Certain surgical repairs such as Burch bladder suspension with posterior colporrhaphy may be associated with increased rates of dyspareunia. Finally, postoperative vaginal stenosis may result from levatorplasty or aggressive trimming of the vaginal mucosa and result in dyspareunia or apareunia.

Another study from 2005 analyzed the practice patterns and determining trends of IUGA members, the authors found that “the preferred primary continence procedure was Tension Free Vaginal Tape (TVT) in one hundred and thirty four (68%) respondents. The preferred secondary continence procedure was colposuspension or Trans obturator tape in twenty-six respondents each (13%). The preferred secondary continence procedure (Table 2) was TVT in a majority (37%) followed a close second by colposuspension (34%) (Jha S. European Urology 2005). Pubovaginal slings, using autologous fascia and cadaveric fascia, proposed by McGuire accounted for 10% of the preferred secondary continence procedures. 96% of respondents were performing TVT. The majority of the respondents were using regional anesthesia (45%) for performing TVT followed by local anesthesia in 33%. General anesthesia was being used only by 21%. A post procedure cough test was done in 60% cases. The predominant surgical procedure of choice is now TVT. This has replaced colposuspension as the primary continence surgery of choice. Since the publication of the recent NICE (National Institute of Clinical Excellence) guidelines on the surgical management of USI, both TVT and colposuspension have been identified as the gold standard surgical procedures in the management of stress incontinence. However as TVT is an easier procedure associated with less morbidity than colposuspension, so is fast becoming more popular. TVT was also more likely to be cost-effective compared to colposuspension as long as the differential inpatient length of stay for women in the TVT group was no more than one day higher than for those who underwent Colposuspension.”

A study from 2009 looking at trends in treatment of SUI from 1979-2004 found that “With the introduction of the tension-free midurethral sling in 1995, pubovaginal slings have become a common first-line outpatient treatment for SUI,” and that “The relative decline in the more traditional suburethral sling procedure (ICD-9-CM, 59.4) and

retropubic urethral suspension (ICD-9- CM, 59.5) likely is due to an increase in the use of midurethral slings, replacing these traditional procedures.” (Oliphant S. AJOG 2009).

Similarly, a study from 2009 identified patterns in the surgical management of women with stress urinary incontinence in the United States from 1992 to 2001 and found that “[t]he 1990s saw a rapid shift in the surgical management of stress urinary incontinence. The rapid increase in utilization of sling procedures corresponded with a decrease in utilization of the many other available anti-incontinence procedures.” (Anger J. Urology 2009).

A study from 2010 analyzing SUI procedures in Belgium from 1997-2007 found a near fourfold increase in the number of SUI procedures that coincided with the introduction of TVT in the Belgian market between 1998 and 2001 (Cammu H. Int Urogyn J 2010). Rates of anti-incontinence surgery increased by 272% in Belgium between 1997 and 2007. “This tension-free placed mesh is relatively easy to install and as effective as the open colposuspension. It causes less morbidity compared to the colposuspension and, therefore, has become the gold standard. The tension-free sling has become very popular throughout the world.” Further, “reasons for the important rise in anti-incontinence surgical procedures may be that the tension-free procedures yield an excellent outcome, are of relatively short duration and require only a brief patient stay in the hospital. Another reason may be the easiness for the practitioner to learn the procedure.”

A 2011 study evaluating trends in inpatient urinary incontinence surgery in the United States between 1998 to 2007 found that the “total number of SUI surgeries performed during this 10-year period was 759,821 (Wu J. Int Urogyn J 2011). The annual number of procedures increased from 37,953 in 1998 to 94,910 in 2007. The type of SUI surgery performed also changed ( $p < 0.001$ ). In 1998, retropubic suspensions represented 52.3%, decreasing to 13.8% in 2007. “Other repair of SUI” (ICD-9 59.79) comprised 22.4% in 1998, increasing to 75.2% in 2007, likely representing midurethral slings. Although numerous incontinence surgeries have been variably popular in recent decades, retropubic colposuspensions and traditional bladder neck slings have proven long-term efficacy. However, these two procedures are not minimally invasive and require an abdominal incision. The midurethral mesh sling, a minimally invasive procedure that can be performed quickly with comparable outcomes to the Burch colposuspension, is now considered by many in the USA to be the new gold standard since its introduction in the USA 10 years ago. In 1998, the most common procedure was retropubic urethral suspension (52.3%) followed by “other repair of SUI” (22.4%) (Table 2). This finding had reversed by 2007, when the most common procedure was “other repair of SUI” (75.2%) followed by retropubic procedures (13.8%) (“other repair of SUI” represents the ICD-9 procedure code 59.79) (Table 2 and Fig. 1). Suprapubic slings remained the third most common procedure at 15.8% in 1998 and 8.2% in 2007.

A 2012 study analyzing SUI surgery data from 2000 to 2009 found that there was a dramatic increase in slings, with a corresponding decrease in Burch procedures from 2000 to 2009. Other SUI surgeries had lower rates (Jonsson Funk M Obstet Gynecol 2012). Thus, in 2009, slings represented 89.1% of all SUI procedures followed by collagen with 4.0%, Burch with 3.8%, and all other SUI surgeries combined with 3.0%.

An 11 center RCT from 2012 found that “approximately 93% of the participants in both groups received a transobturator or retropubic midurethral sling, and midurethral slings are routinely used in patients with either stress incontinence or both stress and urge (mixed) incontinence (Nager C. NEJM 2012). The surgical treatments that were performed in the urodynamic-testing and evaluation-only groups, respectively, were as follows: retropubic midurethral sling in 64.7% and 64.6%, transobturator midurethral sling in 29.0% and 28.1%, mini-sling in 2.0% and 1.4%, traditional sling in 3.4% and 4.9%, retropubic urethropexy in 0.0% and 0.7%, and urethral-bulking injection in 1.0% and 0.4%.”

A study from 2013 analyzing a total of 6,355 nonpediatric urologists applied for certification or recertification between 2003 and 2012 found that “Two-thirds (4,185) reported performing any procedures for female incontinence. Procedures sharply increased from 4,632 in 2003 to 7,548 in 2004, then remained relatively stable between 2005 and 2012 (range, 8014-10,238 cases) (Chughtai B. Female Urology 2013). Traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 to <1% since 2010 ( $P < .0005$ ). Midurethral sling procedures have risen sharply from 3210 procedures in 2003 to 7200 in 2012 ( $P < .0005$ ).” The authors concluded that “Midurethral slings have been widely adopted by urologists over the last decade. Increase in sling usage coincided with a drastic decline in traditional repairs, implying that the newer midurethral slings were replacing these traditional procedures for the treatment of female incontinence.” “The medical, psychological, social, and economic burden of female stress urinary incontinence (SUI) is significant. The more minimally invasive options have gained popularity because of their procedural ease and likely decreased rates of complications. With the apparent proliferation of midurethral slings, we sought to determine the changes in practice pattern of urologists surgically managing SUI in the United States. We conducted an analysis of annual case logs submitted to the American Board of Urology (ABU) for certification and recertification between 2003 and 2012. Of all urologists treating female incontinence, 3878 (93%) reported any use of slings and 2216 (53%) reported using slings exclusively. The present study, which evaluates data from the ABU, shows that midurethral slings and urethral bulking agents are the only procedures performed currently for female SUI, with 5 times as many midurethral slings performed as urethral bulking agents. The treatment for female SUI has evolved over the past decade. The overall number of midurethral slings cases performed for female SUI has doubled. An increased awareness of the problem, an aging population, and the proliferation of synthetic midurethral slings all likely contributed to this trend. Concurrently, there has been a decline in the number of traditional repairs reflecting current urologic training.”

Another study from 2011 evaluated AUGS Members' use of synthetic mesh after the 2011 FDA Public Health Notification (Clemons J. FPMRS 2013). The authors found that "Little change in the use of synthetic or biologic slings was seen after the 2011 FDA safety update. Virtually all members continue to use synthetic mesh for slings, including 90% of members that use mesh in 90% to 100% of sling cases, whereas only 10% use biologic grafts for slings. Table 3: Mesh Sling: 93% (453) – Same use (still using – no change in practice)."

Additionally, a 2013 study compared the effectiveness of mesh versus non-mesh sling surgery in Medicare patients as measured by the frequency of complications with 1 year (Suskind A. ACOG 2013). They identified 6,698 Medicare beneficiaries who underwent mesh sling procedures and 445 Medicare beneficiaries who underwent nonmesh sling procedures. "The overall frequency of complications was similar between the two groups at 69.8% and 72.6% in the mesh and nonmesh groups, respectively. Patients undergoing mesh procedures were less likely than patients undergoing nonmesh procedures to require management for bladder outlet obstruction... and were less likely to have a subsequent sling removal and revision or urethrolysis. Frequencies of most complications were similar regardless of the use of mesh except for the management of bladder outlet obstruction. Surgical technology has evolved tremendously over the past two decades, resulting in the development of procedures with decreased morbidity and faster recovery. These changes have facilitated the migration of select procedures from the hospital outpatient department to the ambulatory surgery center, where they typically can be performed at a lower cost per episode. Anti-incontinence surgery is a perfect example of this shift. With the development of polypropylene mesh for use in midurethral slings in the mid-1990s, rates of sling procedures have dramatically increased, replacing older, more invasive inpatient procedures such as the Burch colposuspension. Between 2006 and 2008, 12,707 slings surgeries were performed, and of these patients, 6,698 (93.8%) and 445 (6.2%) women had procedures using mesh and nonmesh materials, respectively. Table 3: Complications of Mesh and Nonmesh Slings Within 1 Year of Surgery. Any complication: Mesh = 69.8%; Nonmesh = 72.6%; New diagnosis of pelvic pain: Mesh = 6.4%; Nonmesh = 6.2%. First complications occurring within 1 year of hospital-based outpatient sling placement were relatively common regardless of whether mesh was used, although the majority of these were minor. In fact, patients undergoing nonmesh procedures had a less favorable complication profile in that they were more likely to require a subsequent intervention for bladder outlet obstruction, including sling removal and revision or urethrolysis procedures. Our findings are also consistent with the American Urological Association Guidelines that suggest that synthetic slings have similar efficacy and less morbidity than nonmesh surgical techniques."

A 2013 study evaluating trends in the surgical management of SUI from 2002 to 2007 found that surgical management of women with SUI shifted toward a dominance of procedures performed in ambulatory surgery centers from 2002 to 2007, although

the overall number of procedures remained stable (Rogo-Gupta L. Female Urology 2013). Slings remained the dominant surgical procedure, followed by injectable bulking agents, both of which are easily performed in outpatient settings. The past decades have witnessed a shift in the surgical management of SUI toward a dominance of sling procedures. As part of the Urologic Diseases in America Project, we previously analyzed data from Medicare beneficiaries from 1992 to 2001 and found rapid shifts in surgical procedures for female SUI. In 1992, urethropexy (Burch, Marshall-Marchetti-Krantz) was the most commonly performed procedure. However, it was surpassed by the sling and the suburethral bulking procedures by 2001. Similar declines were seen with urethropexy and needle suspensions. Conversely, we demonstrated an increase in slings from among the least commonly performed procedures in 1992 to the most commonly performed procedure in 2001.”

A study from 2014 compared the surgical trends for primary SUI from 2006-2010 vs. 1997-2005 and found that “the follow-up study, midurethral sling (MUS) application increased significantly from 53.09 % in 2006 to 78.74 % in 2010 (Wu J. Int Urogyn J 2014). It was associated concomitantly with a decrease in retropubic urethropexy (RPU) from 29.68 % to 12.99 %, and pubovaginal sling treatment (PVS) from 9.33 % to 3.46 %. MUS was most commonly used among all patients’ and surgeons’ age groups, and different accreditation hospital levels. Of all surgeries 12,351 (81.8 %) were performed by gynecologists, whilst 2,649 (17.5 %) were performed by urologists. Nevertheless, a comparison between the practice patterns of surgeons with different specialties reveals that MUS was the most commonly adopted surgery by both gynecologists (71.38 %) and urologists (57.91 %). During time-frame comparison, MUS increased 2.7 times (68.79 % vs 25.25 %), accompanied by a decrease in RPU 2.3 times (46.84 % vs 20.18 %) and a decrease in PVS 2.8 times (15.96 % vs 5.66 %). MUS significantly increased up to 78 % in 2010, concomitantly decreasing the numbers of RPU and PVS considerably. In a recent review by Cox et al., MUS has been demonstrated to be just as effective as these traditional procedures, e.g., RPU and PVS, but with less associated morbidity, based on randomized controlled trials. Thus, MUS is granted as a new “gold standard” first-line surgical treatment for women with uncomplicated SUI. The choice of surgical procedures may more or less depend on the surgeons’ preferences for the treatment options. As for surgeons’ age, MUS was more commonly used by surgeons aged <50 years, while PVS and periurethral injection were more commonly performed by surgeons aged ≥50 years.”

Another study from 2014 evaluating the current status of SUI treatments in Korea found that the number of surgical cases decreased continuously from 2008 to 2011. However, the number of transvaginal surgeries using a midurethral sling (R3565) increased continuously (Cho SY. Int Neurourol J 2014). Only a few of the SUI surgeries involved the Burch operation and injection therapy (Table 1). The sling procedure has become the most common SUI surgery technique. Table 1: The number of surgical cases according to the year of surgery. Surgeries in 2008 (n = 42,195) were: Synthetic MUS = 39,516 (96%) Autologous fascial sling = 1,358 (3.3%); Burch colposuspension =

103 (0.2%). Surgeries in 2009 (n = 42,166) were: Synthetic MUS = 40,684 (98.6%); Autologous fascial sling = 547 (1.3%); and Burch colposuspension = 47 (0.1%). Surgeries in 2010 (n = 34,787) included: Synthetic MUS = 33,693 (99.3%); Autologous fascial sling = 231 (0.6%); Burch colposuspension = 29 (0.1%). Surgeries in 2011 (n = 33,173) were: Synthetic MUS = 32,166 (99.3%); Autologous fascial sling = 227 (0.6%); and Burch colposuspension = 66 (0.2%).

A study from 2015 evaluating the IUGA members' practice patterns showed that the preferred method of treatment for SUI is the midurethral sling, regardless of prior treatments, concomitant surgeries, or examination findings (Ghoniem G. *Int Urogyn J* 2015). "Synthetic midurethral slings are predominant in the current treatment of SUI." "The treatment of stress incontinence has shifted in recent years, with the initial survey showing a predilection for the Burch colposuspension as a primary and secondary surgical treatment for normal pressure urethral SUI (44 and 41%), while the current survey revealed that 2% of respondents were performing the Burch procedure as a primary SUI treatment and 11% of respondents were using it as a secondary treatment." TVT is the preferred treatment for patients with ISD.

Pelvic organ prolapse and SUI are different health conditions. Surgeries that use mesh to treat these conditions have their own unique risks and benefits. All surgeries carry a risk of side effects. The FDA found that long-lasting side effects from treating SUI with mesh seem to be rare. For patients who choose to have surgery, mesh sling surgery is the most common procedure used. It is a less invasive surgery, and patients tend to recover quicker than with the alternative surgeries to correct SUI. (These alternatives are slings using patients' own tissues and bladder suspension procedures.) The AUA's guidelines list mid-urethral, mesh slings, as a "standard" treatment for SUI. The AUA points to a large number of scientific studies that support the use of mesh slings to treat SUI.

The midurethral sling remains the gold standard surgical repair for treating SUI. "Specifically MUS, which are the predominant SUI surgical procedure and the clear standard of care – remain in the surgeon's armamentarium after the July 2011 FDA safety warning (Nager C. *OBGManag* 2012). A PubMed search of "tension-free vaginal tape" reveals more than 2,000 publications. Midurethral slings and pubovaginal slings had similar cure rates. Pubovaginal slings, however, had more postoperative lower urinary tract symptoms and a higher reoperation rate. Pubovaginal slings require an 8-cm lower-abdominal incision, general or regional anesthesia, and hospitalization (usually). They also have higher risks of intraoperative bleeding and wound complications (including incisional hernias) than MUS. By contrast, MUS require 3 small 1-cm incisions and can be performed on an outpatient basis with local anesthesia and sedation. Postoperative recovery is significantly easier and shorter with MUS than with pubovaginal slings. In this century, the full-length MUS procedures are the predominant SUI surgical procedure and the clear standard of care. Studies have not demonstrated common or significant vaginal pain or pain with intercourse after MUS. I urge you to not

replace on a widespread basis the most studied, safe, and successful treatment for SUI with a procedure that is considerably more invasive and complicated and can be more painful and require a longer recovery. We all must do our best to clear up the confusion created by misleading television advertisements by law firms. Full-length synthetic midurethral slings remain the current standard of care for stress incontinence surgery.”

A 2010 review in the New England Journal of Medicine described that, “[u]ntil recently, the reference standards for incontinence surgery included the Burch retropubic urethropexy and the suburethral fascial sling; however, both require an abdominal incision and are associated with substantial postoperative recovery time and complications (Rogers R. NEJM 2010). The fascial sling is also with higher rates of postoperative complications. Many women are reluctant to undergo either procedure because of the strain that hospitalization and recovery places on their families and jobs. In 1996, Ulmsten et al introduced a synthetic midurethral sling, the tension-free vaginal tape, which could be inserted by means of a minimally invasive surgical procedure. Incisions are small, most procedures are performed on an outpatient basis, and postoperative recovery is rapid.”

In 2012, Lee and colleagues found that midurethral sling (MUS) is the gold standard for stress urinary incontinence (SUI) in the index patient, with equivalent outcomes and minimal adverse events in comparison with traditional SUI procedures (Lee EW. Urol Clin N Am 2012). The midurethral sling (MUS) is now the most commonly performed surgical treatment for stress urinary incontinence (SUI). It is considered the gold standard for patients with genuine SUI. Encouraged by the excellent outcomes and low morbidity in these index patients, clinicians have extended the use of the MUS to treat SUI in more complex situations, such as recurrent SUI, mixed urinary incontinence (MUI), and SUI in the elderly or obese. In 1997, the AUA Female Stress Incontinence Clinical Guidelines Panel concluded that the retropubic suspensions and pubovaginal sling (PVS) were the most effective treatments for SUI, reflecting the widespread sentiment that these procedures represented the gold standard at that time. Only 2 years earlier, Ulmsten and Petros first described the tension-free vaginal tape (TVT), a retropubic midurethral synthetic sling that was considerably less invasive with high short-term success rates. Because of the relative ease of performance and very good initial results, it quickly became one of the most commonly performed procedures and inspired the development of various other MUSs. Several RCTs have confirmed their findings, culminating in the most recent meta-analysis by Novara and colleagues, which found that the MUS is more effective than the Burch colposuspension and equally as effective as the PVS in achieving objective cure of SUI. Thus, the MUS has effectively been established as the new gold standard for surgical treatment of SUI. Overall summary of Cochrane meta-analysis for retropubic and transobturator slings. For retropubic versus transobturator approach: retropubic slings have a slightly higher objective cure rate (88% vs 84%), but there is no difference in subjective cure rate (83% for both groups in the Cochrane meta-analysis). The Pubovaginal Sling has traditionally been identified as the procedure of choice after failed incontinence surgery based on its

superior efficacy over colposuspension, and in this setting reported cure and improvement rates have ranged from 59% to 86%, but data have been lacking on its use in the MUS era. Midurethral slings have become the most commonly performed procedures for stress urinary incontinence in North America. Management of vaginal erosions can be straight forward and simple. The midurethral sling will continue to be extensively utilized in the foreseeable future. Surgical choice between retropubic and obturator versions is driven by surgical experience and patient selection.

A 2012 review noted that “almost all surgical procedures for stress urinary incontinence performed today involve placement of a retropubic or transobturator midurethral synthetic sling (Walters M. OBGManag 2012). Today, virtually all of these operations have been replaced in general practice by retropubic or transobturator (TOT) midurethral synthetic slings. Although Burch colposuspension and the pubovaginal fascial sling procedure are effective for both primary and recurrent SUI, they are more invasive than midurethral slings, cause more voiding dysfunction, and have significantly longer recovery times, making them less attractive for most primary and recurrent cases of SUI. The evolution of SUI surgeries has shifted so far toward midurethral slings that Burch colposuspension and the pubovaginal sling procedure are rarely performed or taught in obstetrics and gynecology or urology residency programs. Compared with synthetic slings, fascial slings are effective but take longer to place and have a higher rate of surgical morbidity and more postoperative voiding dysfunction. They are now mostly indicated for complex recurrent SUI, usually managed by specialists in female pelvic medicine and reconstructive surgery. Current slings are lightweight polypropylene mesh. Most slings today are tension-free midurethral slings consisting of synthetic, large- pore polypropylene mesh. Mesh exposures occur with similar frequency for the different sling types as long as large-pore lightweight polypropylene is used. Dehiscence of the suburethral incision (mesh exposure) is uncommon with midurethral slings, occurring in 1% to 2% of patients. Dehiscence can be managed with estrogen cream or trimming of the exposed portion of the sling in the office.

A 2013 review by Cox reviewed a number of Cochrane Reviews and found that “the traditional gold standards of Burch retropubic colposuspension and pubovaginal slings are still appropriate treatment options for some patients, but randomized controlled trials have demonstrated that synthetic midurethral slings are just as effective as these traditional procedures but with less associated morbidity. Thus, midurethral slings— inserted via a retropubic or transobturator approach—have become the new gold standard first-line surgical treatment for women with uncomplicated SUI.” (Cox Nature 2013). The review noted that retropubic MUSs are effective for patients with mixed urinary incontinence. “Based on the literature a new gold standard first-line surgical treatment for women with SUI is the synthetic midurethral sling inserted through a retropubic or transobturator approach.” “Synthetic midurethral sling procedures were first developed by Ulmsten in 1995, since which time they have become the most commonly performed procedure for female SUI. The reasons for this are multiple: the procedures are performed relatively quickly, are easy

to learn, and have acceptable rates of morbidity. More importantly, there are now long-term data to show that they compare favorably to the traditional methods of surgical repair for SUI detailed above.”

#### **X. Ultrapro is Not a Safer Alternative Design for TVT or TVT-O:**

Some of plaintiffs’ experts have speculated that the use of a partially absorbable mesh, such as Ultrapro or Vypro would be a safer alternative material than the TVT mesh for treating stress urinary incontinence. They rely on the Okulu (2013) study which is not a well-powered study and did not directly compare the hand-made (mechanically cut) Ultrapro pubovaginal sling to TVT or TVT-O. These claims are without reliable scientific support.

#### **XI. The Benefits of TVT Outweigh the Risks of Harm:**

The AUA Position Statement approved in 2011 and revised in 2013 noted the following about the safety profile and utility of synthetic midurethral slings such as TVT:

- Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction.
- Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.
- Additionally, both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the AUA support the use of multi-incision monofilament midurethral slings for the treatment of SUI in properly selected patients who are appropriately counseled regarding this surgical procedure by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.

- Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh sling techniques.

AUGS (with over 1,700 members) and SUFU (with over 500 members) adopted a joint position statement in 2014 highlighting the following about the safety and efficacy of midurethral slings:

- The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.
- Developed in the early 1990's, midurethral slings (MUS) treat stress urinary incontinence (SUI) in a minimally invasive, generally outpatient procedure.
- Polypropylene material is safe and effective as a surgical implant. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years. [Referencing Nilsson's 17 year TVT study].
- The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history. A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently

demonstrated its clinical effectiveness and patient satisfaction. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

- Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients. Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members.

AUGS and SUFU also issued Frequently Asked Questions for Providers and Patients to convey the following information about Midurethral Slings:

- A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing mid-urethral slings in the treatment of SUI... Numerous randomized, controlled trials comparing types of midurethral slings, as well as comparing MUS to other established SUI procedures, have consistently demonstrated its clinical effectiveness and patient satisfaction. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy. This includes a recent 17 year follow-up study. No other surgical treatment for SUI before or since has been subject to such extensive investigation.
- The MUS is the most studied anti-incontinence procedure in medical history. Furthermore, it is likely that more individuals have undergone this surgical procedure for the treatment of SUI than any other. The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury,

dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract.

- Currently available mid-urethral slings are composed of macroporous, knitted, monofilament polypropylene, sometimes known as “Type I” meshes.... Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world.... As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [Nilsson’s 17 year study].
- All midurethral slings available in the US are made of polypropylene knitted into a macroporous mesh.
- Does the MUS mesh made of polypropylene degrade over time? Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with “cracked” surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.
- Two large government funded studies have evaluated the mid-urethral sling’s safety and efficacy – both found the procedure to have a low complication rate and a high success rate. Other large scientific studies from around the world have supported the safety and efficacy of the mid-urethral sling.
- A peer-reviewed scientific article reported on the safety outcomes of the mid-urethral sling in Sweden over a 17 year period. It found a high satisfaction rate and no serious long-term adverse events related to the mid-urethral sling.
- Alternative surgical treatment options to the mid-urethral sling have been performed by surgeons for over 100 years.... In general however, the mid-urethral sling has been found to be as or more effective than any of these procedures and is as durable (the surgery maintains its favorable effects over a longer period of time). In addition, the pain related to the procedure, the time required to recover from the surgery, and time to return to normal activities including work is less for the mid-urethral sling than for any of these surgical procedures.

- There is no evidence that any women have developed cancer as a result of a mid-urethral sling.

IUGA approved a similar position statement in 2014 describing the safety and efficacy of midurethral slings:

- Stress urinary incontinence is a common, burdensome and costly condition for women with a negative impact on quality of life.
- Mid-urethral slings are minimally invasive procedures developed in Europe in the 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities together with lower rates of complications. This has resulted in MUS becoming the operation of choice in Europe, Asia, South America, South Africa, Australasia and North America for treatment of SUI with several million procedures performed worldwide.
- There is robust evidence to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications. For MUS these include bleeding, damage to the bladder and bowel, voiding difficulty, tape exposure and pelvic pain; all of these may require repeat surgery but this is uncommon. Nevertheless, the results of a recent large multi-center trial have confirmed excellent outcomes and a low rate of complications to be expected after treatment with MUS. Additionally, long term effectiveness of up to 80% has been demonstrated in studies including one which has followed up a small group of patients for 17 years.
- As a result, IUGA supports the use of monofilament polypropylene mid-urethral slings for the surgical treatment of female stress urinary incontinence.

Furthermore, IUGA also published guidelines for research and clinical practice in 2008 noting the complications that are related to surgical procedures for SUI:

- Complications listed below related to SUI surgical procedures can potentially involve any of the organs of the pelvis include: Bladder injuries, Urethral injuries, Ureteral injuries, Intestinal injuries, Erosions, Hemorrhage, Fistulae, Prolapse,

Voiding dysfunction, Postoperative OAB, ISD, Recurrent incontinence, Dyspareunia, and Pain.

- Intravesical sutures have been reported in almost all SUI surgical procedures. These patients often present with bladder or pelvic pain, frequency, urinary tract infection, or recurrent incontinence.
- Miscellaneous complications reported after the Burch procedure, include massive hemorrhage requiring transfusion, hematoma, bladder injuries diagnosed intraoperatively and postoperatively, ureteral kinking, urinary retention, wound infection, pelvic abscess, UTI, and DVT.
- Voiding dysfunction such as frequency, nocturia, urgency with and without incontinence, hesitancy, retention, incomplete emptying, and recurrent urinary tract infections have been reported after all anti-incontinence procedures. Voiding dysfunction after retropubic colposuspension and mid-urethral sling procedures is usually transient and resolves postoperatively. The incidence of de novo detrusor overactivity and urge urinary incontinence varies depending upon the anti-incontinence procedure with rates as high as 33%. Comparing retropubic vs TO slings, the incidence of urge urinary incontinence and detrusor overactivity rates are lower after TO slings.
- It is clear, however, that after all anti-incontinence surgeries, erosion and migration of suture material, bolsters, supporting tacks, and synthetic mesh material can occur.
- The type of mesh material used in mid-urethral slings and prolapse surgery is of importance as some materials demonstrate higher erosion and extrusion rates than others. Higher rates are reported with synthetic mesh that is woven with small pore size, as macrophage migration to deposit collagen and engulf bacteria is hindered (e.g., ObTape and GoreTex). Fortunately, these materials have been replaced with loosely knitted, macroporous (>75 µm), monofilament polypropylene material with lower complication rates. Mesh extrusion is usually treated with local excision in the office setting.

Australian and New Zealand societies endorsed the synthetic midurethral sling as well in a 2014 position statement from RANZOG and USGA:

- In Australia, the midurethral sling has been the operation of choice to treat female SUI since 2004. RANZCOG and UGSA support the use of monofilament polypropylene mid-urethral sling for surgical treatment of female stress urinary incontinence.

In a 2013 Position Statement related to meshes for pelvic organ prolapse, AUGS clarified that “Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress incontinence surgery.”

The National Institute of Health Care and Excellence set forth criteria for treating stress urinary incontinence in the 2013 Guideline, including:

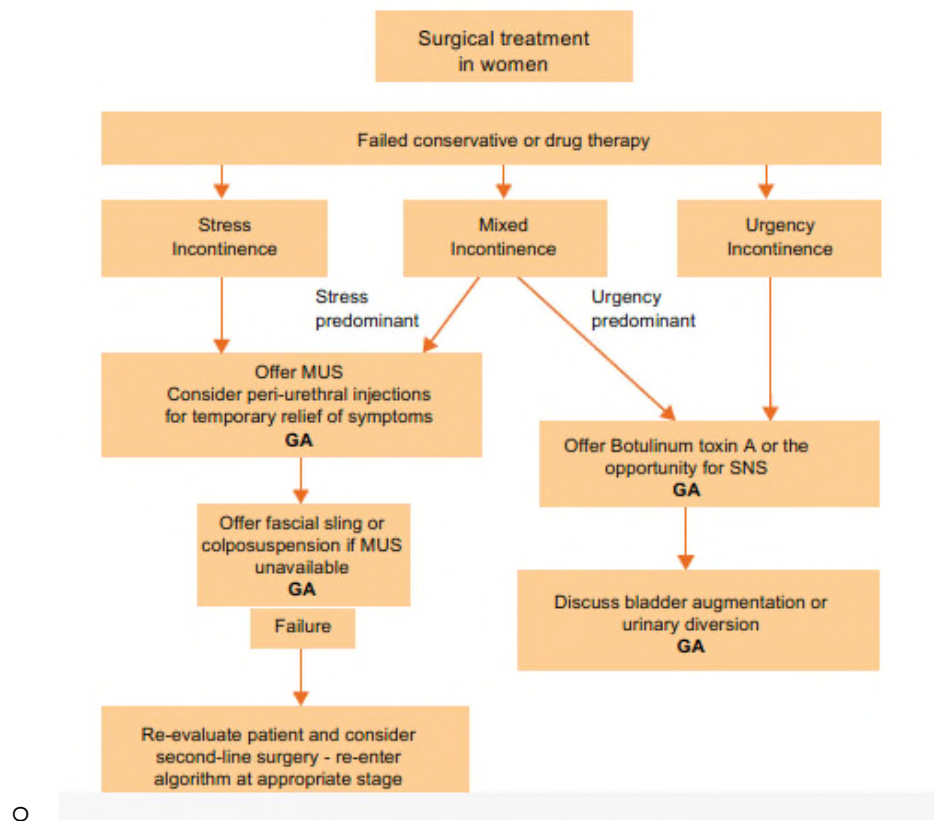
- Section 1.10.2: If conservative management for SUI has failed, offer: synthetic mid-urethral tape; open colposuspension; autologous rectus fascial sling.
- Section 1.10.3: Synthetic tapes: When offering a synthetic mid-urethral tape procedure, surgeons should: use procedures and devices for which there is currently high quality evidence of safety and efficacy [Footnote 11: The guideline only recommends the use of tapes with prove efficacy based on robust RCT evidence... TVT for retropubic approach; TVT-O for an “inside-out” transobturator approach....
- Section 1.10.9: Colposuspension. Do not offer laparoscopic colposuspension as a routine procedure for the treatment of stress UI in women.
- Section 1.10.10: Biological Slings: Do not offer anterior colporrhaphy, needle suspensions, paravaginal defect repair and the Marshall-Marchetti-Krantz procedure for the treatment of stress UI.

The European Association of Urology’s 2012 Guidelines for treating urinary incontinence found that:

- The effectiveness of colposuspension deteriorates over 5 years, and there is a higher rate of genitourinary prolapse than with other operations. Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and postoperative urinary tract infection (UTI).
- There has been a rapid adoption of midurethral synthetic sling insertion as the first-line surgical option for SUI because it is effective, it is less invasive, and patients recover more quickly.
- Midurethral sling insertion was associated with a lower rate of new symptoms of urgency and voiding dysfunction compared with colposuspension.
- Recommendations:

- Offer midurethral sling to women with uncomplicated stress urinary incontinence as the initial surgical intervention whenever available.
- Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if midurethral sling cannot be considered.
- Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterization; ensure they are willing and able to do so.

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The AUA Guideline for treating incontinence noted in 1997 that “Surgeons now recognize the importance of not making slings overly tight, because of the relationship between excessive tension and complications.” Additional updates occurred in 2009 and 2012. The AUA Panel Members performed a meta-analysis of the literature, with updates in 2009 and 2012, and determined that:

- Surgeons should take these considerations into account, together with their own areas and levels of expertise and their own previous treatment results, when counseling patients regarding choice of procedure.

- Stress urinary incontinence (SUI) has a significant impact on the quality of life for many women... Many women in the United States (U.S.) elect to have a surgical procedure for management of their SUI symptoms each year.
- The midurethral slings had an efficacy comparable to autologous slings in the surgical treatment of SUI.
- There are complications that may occur that are unique to specific mesh materials; however, these complications appear to be rare. Intraoperative use of cystoscopy can be performed to minimize the risk of urinary tract injury or erosion. See also studies by Demirci (2001) and Galloway (1987) reporting on Burch complications.
  - Table 1: Cure Rates:
    - Burch at 12-23 mo = 81%; at 24-47 mo = 76%; at  $\geq 48$  mo = 73%
    - AFS at 12-23 mo = 90%; at 24-47 mo = 81%; at  $\geq 48$  mo = 82%
    - MUS 12-23 mo = 84%; at 24-47 mo = 81%; at  $\geq 48$  mo = 84%
  - Table 3: De novo urge incontinence:
    - Burch 8%
    - AFS 9%
    - MUS 6%
  - Table 4: Retention:
    - Burch 3%
    - AFS 8%
    - MUS 3%
- Appendix A11:
  - Burch:
    - Pain = 6%
    - Sexual Dysfunction = 3%
    - Voiding Dysfunction = 10%
  - Autologous Fascial Sling:
    - Pain = 10%
    - Sexual Dysfunction = 8%
    - Voiding Dysfunction = \* (only case reports of this complication exist, and data are insufficient to estimate the frequency).
  - MUS:
    - Pain = 1%
    - Sexual Dysfunction = 0%
    - Voiding Dysfunction = 2%

The International Continence Society (ICS) has also issues a Fact Sheet on Urinary Incontinence, which includes the following:

- Definitive therapy for SUI is surgical and involves restoring urethral support through use of a sling. Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands. Various techniques for sling placement and different meshes are employed according to physician preference, but all appear to be equally effective.
- SUI remains a common and distressing condition that adversely affects quality of life.
- There are no approved pharmacologic agents for SUI.

The FDA has looked at the issue of safety and efficacy related to midurethral slings and found the following in a 2013 statement on considerations about surgical mesh for SUI that:

- The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year.
- The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI repair, which is mesh erosion, also known as extrusion.
- Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of mesh erosion, it may be necessary to return to the operating room to remove part or all of the mesh.

ACOG and SUFU updated the practice bulletin “urinary incontinence in women” in 2015. The purpose of this joint document of the American College of Obstetricians and Gynecologists and the American Urogynecologic Society is to review information on the current understanding of urinary incontinence in women and to outline guidelines for diagnosis and management that are consistent with the best available scientific evidence. The professional societies found the following:

- Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women (67). Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension (68–70). Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings (68). Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings (69). For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women (67, 71). However, in women who decline or are not candidates for synthetic mesh slings, autologous fascial bladder neck slings and Burch colposuspension (laparoscopic or open) remain effective treatment options.
- Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Uro-dynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the “standard of care” in the surgical treatment of stress urinary incontinence (72).
- Although there are many ways to place midurethral slings, the main approaches used are retropubic and trans-obturator techniques. Evidence from a 2015 systematic review demonstrates that these approaches are effective and appear to be comparable in terms of efficacy and patient satisfaction (73). Subjective cure rates up to 1 year after surgery were similar and ranged from 62% to 98% (transobturator route) and 71% to 97% (retropubic route). Short-term objective and long-term (more than 5 years) subjective and objective cure rates also were similar. Voiding dysfunction, bladder perforation, major vascular or visceral injury, and operative blood loss were more common with retropubic slings, whereas groin pain was more common with transobturator slings. Mesh complications (eg, exposures, erosions) were uncommon and did not differ between routes of sling placement (2% overall).
- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.
- The risk-benefit profile for each procedure, along with the patient's goals and expectations, should be considered in determining the preferred sling type for each individual.

## **XII. Conclusion:**

In conclusion, the TVT and TVT-O have revolutionized health care for women by providing a less invasive, durable, quicker, and safer treatment option for women seeking surgical treatment for stress urinary incontinence. TVT quickly became the gold standard after withstanding the scrutiny of level 1 RCTs, which have repeatedly duplicated the early TVT results of high cure rates and low complications. Because TVT is the best-studied device, mesh, and procedure for the treatment SUI, surgeons are confidently able to recommend TVT and TVT-O as the first-line surgical treatment for SUI.

Signed March 1, 2016



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